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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,786	05/01/97	BARKATS M	ST94065-US

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/776,786	Applicant(s) Barkats et al.
	Examiner Scott D. Priebe, Ph.D.	Group Art Unit 1819

☒ Responsive to communication(s) filed on *Feb 11, 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *27-55* is/are pending in the application.

Of the above, claim(s) *32 and 33* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *27-31 and 34-55* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 27-31 and 34-55, drawn to adenovirus comprising coding sequence for glutathione peroxidase, gene therapy using same, cells transfected with same and implants comprising cells transfected with same.

Group II, claim(s) 32-33, drawn to adenovirus comprising antisense to glutathione peroxidase gene.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: For the invention of group I, the adenovirus comprises sequences encoding a glutathione peroxidase, which sequence is the special technical feature of group I. For the invention of group II, the adenovirus comprises sequences expressing an antisense inhibitor of glutathione peroxidase, which sequence is the special technical feature of group I. Therefore, each group relies on very different special technical features.

During a telephone conversation with Paul Felner for Martin Savitsky on 12/8/97 a provisional election was made with traverse to prosecute the invention of Group I, claims 27-31 and 34-55. Affirmation of this election must be made by applicant in responding to this Office action. Claims 32 and 33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

The first sentence of the specification should state that the application is --a 371 application of PCT/FR95/01002 filed July 26, 1995--

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, applicant cannot rely upon the foreign priority papers to overcome rejections over the prior art because a certified translation of said papers has not been made of record. See MPEP § 201.15.

Information Disclosure Statement

The information disclosure statement filed 3/6/97 fails to fully comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent or publication listed that is not in the English language. Consequently, reference PD, Dr[illegible]os et al., has been placed in the application file, but the information referred to therein has not been considered.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: there is no antecedent basis in the disclosure for the term "respiratory distress syndrome (ADRS)" recited in claim 43.

The disclosure is objected to because of the following informalities: The sentence bridging pages 2-3 is grammatically incorrect, and makes little sense. On page 8, line 12, it is unclear what "DNA8" refers to.

Appropriate correction is required.

Claim Objections

Claims 28-31, 34-42, 45-47, 49, 50 and 52-55 are objected to because of the following informalities: In dependent claims 28-31, 34-41, 45-47, 49, 50 and 52-55 56-59 should begin with --The--, not "A" or "An"; in claim 42, "an adenovirus" should be --the adenovirus--; and in claim 51, "a cell" should be --the cell--. In claim 55, "fibres" should be --fibers--. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 48-55 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 52-59 are directed to transfected cells and implants comprising same and read on cells and implants present in a human subject wherein the host cells are either part of the human or were derived from that subject before being implanted back into

the human subject. Thus the claim would in essence read upon an integral part of the human subject or the subject as a whole, which is non-statutory subject matter. Limiting the claims to isolated or cultured cells and implants comprising cells *ex vivo*, or limiting the claims to non-human cells or implants comprising non-human cells would overcome this rejection.

Claim Rejections - 35 USC § 112

Claims 27-31 and 34-55 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The various embodiments of the invention broadly include DNA encoding any unspecified glutathione peroxidase, whereas the specification provides a source for the sequence of only a single human glutathione peroxidase cDNA, while this enzyme is probably ubiquitous to almost all aerobic organisms and in at least some animals there are at least four different glutathione peroxidases (see specification at page 4); and MLP, CMV, or RSV-LTR promoters, where the specification provides neither definitions for these abbreviations nor the sequence of each.

An adequate written description of a DNA, such as the instantly recited DNA encoding glutathione peroxidase and promoter sequences, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining

the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606. It is not sufficient to define DNA solely by its principal biological property, i.e. encoding a glutathione peroxidase or MLP, CMV, or RSV-LTR promoters, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. A definition by does not suffice to define the genus because it is only an indication of what the DNA does, rather than what it is. See *Fiers*, 984 F.2d at 1169- 71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such DNA sequences may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984).

Consequently, the specification lacks an adequate written description of generic DNA encoding glutathione peroxidase or bovine glutathione peroxidase or gDNA enoding any glutathione peroxidase, including human, and of RSV-LTR, MLP and CMV promoters, each of whose identity is unclear. In the case of the E1a, this indicates a known structure evident from the specification as being the endogenous adenovirus promoter of the E1a region, whereas for the other DNA sequences, either the identity is uncertain due to undefined abbreviation and/or it is

unclear for generic sequences whether the sequences for a representative sampling of species in the genus are known such that the structures of each genus of sequences can be defined thereby.

Claims 27-31, 34-41 and 48-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant Ad2 or Ad5 adenovirus comprising the cDNA encoding the glutathione peroxidases disclosed by Mullenbach et al. (cited at page 5, lines 1-5 of the specification) under control of the E1a promoter and cultured or isolated mammalian cells infected with same, does not reasonably provide enablement for any other adenovirus vector, glutathione peroxidase encoding DNA or generic viral promoters or specific promoters which are the RSV-LTR, MLP and CMV promoters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In addition, claims 42-47 and 51-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to broadly recited adenoviral vectors comprising DNA encoding a broadly recited glutathione peroxidase, cells infected with the vector, and implants comprising the infected cells, and method of using the vector for the treatment of neurodegenerative diseases. The specification teaches that the claimed products are to be used for either *ex vivo*

gene therapy, e.g. the cells and implants, or *in vivo* gene therapy, which would encompass the adenovirus, pharmaceutical compositions, cells transfected *in situ* in an organism, and method for the treatment of neurodegenerative diseases and possibly other diseases (specification, paras. bridging pages 2-3 and 11-12; page 3, lines 15-19; and page 16, lines 18-25). Since the specification must enable the use of these products and the only utility taught is gene therapy, gene therapy using these products must be fully enabled by the specification, unless the product has another utility readily apparent to one skilled in the art. While one may argue that the adenovirus and transfected cells can be used simply to produce glutathione peroxidase *in vitro,* there is no readily apparent non-therapeutic utility for either the pharmaceutical compositions or the implants, or *in vivo* infected cells. However, for all claims, including those drawn to adenoviruses and transfected cells, the specification fails to enable how to make the products commensurate in scope with the claimed invention.

The specification teaches that the invention can be used to treat neurodegenerative diseases, which include Parkinson's disease, Alzheimer's disease, Huntington's disease and ALS, and other diseases or conditions such as trisomy 21, atherosclerosis, cardiovascular disease, cirrhosis or the liver, diabetes, the formation of cataracts, cranial traumas, neoplasms, and the aging process. No nexus is provided in the specification between either the causes or symptoms of any of these diseases and any preventative, palliative or curative effects that may result either from the intracellular production or secretion of glutathione peroxidase as the result of either *in vivo* or *ex vivo* gene therapy. Rather, the specification that free radicals "may be responsible for"

a variety of diseases or conditions that the prior art teaches were due to other causes. The specification provides little detail on how the invention should be used for its stated purpose, to treat neurodegenerative disease and other diseases. The specification directs the skilled artisan to determine the effective dose empirically, and provides a fairly complete list of all commonly used administration routes from which to choose, with no discussion as to which routes would be suitable or effective for the treatment of specific diseases or conditions. There is no specific guidance provided for treatment of any specific disease or condition, and the etiology and effective treatment of each would be expected to be quite different each one from the others. The specification provides no working examples of the claimed method or the disclosed use of the claimed cells or implant. With respect to the disclosed use for the claimed products and the claimed method, the specification does not teach what level of glutathione peroxidase would constitute an effective level to effect the desired treatment or how long the level would need to be maintained. The specification also fails to disclose any therapeutic endpoint or any methodology for determining whether a particular treatment protocol was successful.

The prior art is silent on the treatment of any disease or condition with glutathione peroxidase or by gene therapy with a vector expressing glutathione peroxidase. With respect to diseases of the brain, Akli et al. teach infection by recombination-deficient, recombinant adenovirus of brain neurons is highly localized to the area of injection (para. bridging pages 224-225). Ricordi et al. teach that gene therapy of central nervous system disorders are difficult in application because most disorders are probably multifactorial and multigenic and the target cells

are located in sites that are not easily accessible. The specification does not teach what area of the brain the claimed products would need to be administered to for treatment of diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, ALS, cranial traumas and cerebral ischaemia, and the blood brain barrier would be problematic for any type of systemic administration to the brain.

Gene therapy was, at the time the invention was made, and still is, an undeveloped and highly unpredictable therapeutic modality, despite a high level of skill in the art. Orkin et al. reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (Orkin et al., pages 1-2). Orkin et al. discloses that pre-clinical trials of adenoviral vectors revealed that the magnitude of the host response to adenoviral vectors was underestimated (page 14, 3rd bullet). Verma et al. (1997) reiterate the finding that not a single

successful gene therapy protocol has been described in the art (Verma et al., page 239, para. 2), and reinforces the considerable problem posed by the immune system to any effective treatment using adenoviral vectors (Verma et al., page 241, col. 1-2). Marshall also discloses the considerable barrier to adenoviral-based gene therapy imposed by the immune system has been and continues to be a fundamental problem. This problem limits the dose range that can be employed, in that if the dose is low, the treatment is inefficient and if the dose is high the vector causes acute inflammation (Marshall, page 1052, col. 2 of box at bottom of page). Crystal also discusses the immunological barrier to adenoviral-based therapy, and also states that adenoviral vectors had been used only in human *in vivo* trials (Crystal, para. bridging pages 404-405), i.e. the prior art is silent on the use of adenoviral gene therapy vectors in any non-human animal.

In addition to the issue of using the claimed products in gene therapy, the specification does not provide an enabling disclosure for making the claimed products, specifically with respect to the adenoviral vectors, commensurate in scope with the claims. The claims are broadly drawn to or limited to any adenovirus comprising DNA encoding any glutathione peroxidase or derivatives thereof, with specific classes of embodiments wherein the promoter used to express the glutathione peroxidase is a MLP, CMV, or RSV-LTR viral promoter. In the case of the promoters, the specification does not define what these promoters are, i.e. the meaning of the abbreviations is not provided..

With respect to adenoviruses, vectors based on the human Ad2 and Ad5 viruses are well known in the art for cloning and expressing heterologous genes, and working candidates in the

development of gene therapy protocols. However, it is not clear whether the prior art discloses sources or sequences for the other mammalian and avian adenoviruses listed on page 11 of the specification, or how these vectors can be used or manipulated to provide the necessary expression vectors, e.g. CAV2. Clearly the specification does not provide the skilled artisan with the information necessary to use these other adenoviruses to make the vectors without either extensive characterization of known isolates or isolation of as yet unknown isolates of "adenovirus". Rather, the knowledge is assumed, i.e. left to the prior art for assistance.

With respect to DNA, cDNA and gDNA, encoding glutathione peroxidase or derivatives thereof, the specification provides no source for this DNA for any species and cites a source for the sequence of only the cDNA of one of the at least four human glutathione peroxidases as disclosed by Mullenbach et al. Although unknown, it is presumed that this enzyme might potentially be found in virtually any aerobic organism, and the claim would encompass the use of the DNA from any such source. The specification indicates that four different glutathione peroxidase proteins had been isolated from different tissues of man, but not in what other organisms or whether the DNA for each was known, including those of man. With respect to derivatives of glutathione peroxidase, the specification provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions substitutions, would be permissible in any such protein that would improve or would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and

biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, pp. 433 and 492-495). Rather the specification implies excessive trial and error experimentation to provide the necessary derivatives to determine which of the high number of sequences encompassed by the claims could be used for the disclosed purposes. As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a

single amino acid sequence and nucleotide sequence having the necessary properties for the disclosed uses, i.e. the natural human glutathione peroxidase.

With respect to the various promoters, it is unclear what some of the recited promoters are, defined only by abbreviation, which would preclude any attempt at isolating them, and second, the specification provides no sequence information or sources of any promoter or secretion sequence with the exception of a single secretion sequence. In the case of the E1A promoter, presumably of Ad2 or Ad5, this promoter is well known in the art. However, for the other promoters, it is unclear whether sources or nucleotide sequences of these elements are known. It is certain that for the more generally claimed viral promoters, only a relative handful of all such sequences encompassed by the claims are known. It is also certain that there would be little or no sequence identity expected to exist between all of the possible viral promoters. To utilize such promoters throughout the scope claimed, one would have to isolate each individually as there is little or no expected sequence identity between even homologous promoters from widely diverse sources, which presumably would encompass any metazoan with neurons. Such excessive experimentation, for which there is no suitable methodology disclosed in the specification, would require excessive experimentation with an inventive contribution.

It has been established by legal decision that a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must

be provided in order to enable the skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement under 35 USC 112, first paragraph. The instant specification does not simply lack minor details but provides little more than an invitation to excessive experimentation with respect to the claimed invention in its various embodiments.

Therefore, in light of the extremely limited guidance provided by the specification, the lack of working examples, the highly undeveloped and unpredictable state of gene therapy at the time the invention was made, and the problems associated with adenoviral-based gene therapy specifically and lack of experience in treatment of non-human animals with adenoviral vectors, it would clearly require undue experimentation for the skilled artisan to use the claimed invention for the only uses disclosed in the specification or to make the claimed products commensurate in scope with the claims.

Claims 29, 35-39, 43 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29 and 38 are indefinite for recitation of "gDNA"; this term is vague since an abbreviation may have more than one meaning. This rejection would be obviated by amendment of the claim(s) to recite --(genomic DNA)-- after the first appearance of "gDNA" .

Claim 35 recites the limitation "the signal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 36-38 are indefinite for recitation of "E1A", "MLP", "CMV" or "RSV-LTR"; these terms are vague since an abbreviation may have more than one meaning. For example, "RSV" could mean respiratory syncytial virus or Rous sarcoma virus. Some of these abbreviations have not been defined in the specification, and amendment of the specification and/or claims to provide the terms for which these abbreviations stand may introduce new matter. Consequently, evidence other than support present in the original specification may be required to establish that the abbreviation refers to a specific term.

Claim 39 recites the limitation "the genome" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 43 is indefinite for recitation of "ALS"; this term is vague since an abbreviation may have more than one meaning. This abbreviation has not been defined in the specification and amendment of the specification and/or claims to provide the terms for which these abbreviations stand may introduce new matter.

Claim 43 is indefinite for reciting an improper Markush group which is to list neurodegenerative diseases. It is unclear why trisomy 21, atherosclerosis, cardiovascular disease,

cirrhosis or the liver, diabetes, the formation of cataracts, cranial traumas, respiratory distress syndrome (ADRS), cancers and the aging process are listed; these are not "neurodegenerative" diseases, as the term would be understood in the art. Also, "the aging process" and "cardiovascular disease" include "diseases" that are also listed, which renders the claim indefinite. The term "neurodegenerative disease" is singular, while some members of the Markush group are plural, which is grammatically incorrect.

Claim 53 is indefinite as it is grammatically incorrect; "gelling compound" is singular, while "glucosaminoglycans" and "lectins" are plural.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 28, 30, 31, 34-39, 41, and 48-50 are rejected under 35 U.S.C. 102(b)/103(a) as being unpatentable over Kahn et al. in view of Mullenbach et al. (UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988).

Kahn et al. disclose replication-defective, recombinant adenoviral vectors for transfer of heterologous sequences into cells of the central nervous system and cells transfected with the vectors. Kahn et al. discloses that the adenoviral vectors are useful for study and regulation of cloned genes in cells or test animals, and for therapy in man or animal involving the production of a protein product of interest (para. bridging pages 1-2); that replication deficient adenoviral vectors are particularly useful for expression of heterologous products in cells of the central nervous system, e.g. glial cells (page 2); that derivatives of human Ad2 or Ad5 are particularly

useful; that for expression of the heterologous DNA, viral promoters such as the MLP promoter of Ad2, the adenovirus E1a promoter, the Rous sarcoma virus-LTR promoter, and the promoter of the IE gene of CMV are particularly preferred for controlling transcription expression (page 4, line 16 to page 5, line 6). The reference does not teach glutathione peroxidase as a desired protein, whose encoding DNA could be incorporated into the disclosed adenoviral vectors.

However, Mullenbach et al. teach the cDNA sequences of both a bovine and human glutathione peroxidase (page 315-317, Fig. 1), and illustrate that glutathione peroxidase is a protein of interest.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate cDNA encoding a human or bovine glutathione peroxidase, taught by Mullenbach et al., into the adenoviral vectors and subsequently infected cells taught by Kahn et al. with a reasonable expectation of success as only routine techniques would be required, and for the express reason that Kahn et al. taught that the vectors were useful for recombinant expression of a protein of interest and Mullenbach et al. illustrate that glutathione peroxidase is a protein of interest.

Claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 are rejected under 35 U.S.C. 102(e)/103(a) as being unpatentable over McClelland et al., U.S. 5, 543,328 in view of Mullenbach et al. (UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988).

McClelland et al. disclose recombinant adenoviral vectors as gene delivery vehicles (col. 1, lines 4-5), e.g. based on Ad5 (see claim 5), that are defective in replication due to deletion of the E1 region and optionally parts of the E2 and E4 regions (col. 4, lines 13-28). The vectors comprise DNA encoding a protein of interest, particularly of therapeutic interest, under control of the major late promoter (MLP), or CMV promoter (col. 3, lines 23-34). Cells which can be transfected include human cells and fibroblasts, myoblasts, endothelial cells, hepatocytes, keratinocytes, and brain and other neural cells. It does not teach that glutathione peroxidase is a protein of interest.

However, Mullenbach et al. teach the cDNA sequences of both a bovine and human glutathione peroxidase (page 316-317, Fig. 1), and illustrate that glutathione peroxidase is a protein of interest.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate cDNA encoding a human or bovine glutathione peroxidase, taught by Mullenbach et al., into the adenoviral vectors and subsequently infected cells taught by McClelland et al. with a reasonbiae expectation of success as only routine techniques would be required, and for the express reason that McClelland et al. taught that the vectors were useful for recombinant expression of a protein of interest and Mullenbach et al. illustrate that glutathione peroxidase is a protein of interest.

Claims 36-38 and 50 are rejected under 35 U.S.C. 102(e)/103(a) as being unpatentable over McClelland et al., U.S. 5, 543,328 and Mullenbach et al. (UCLA Symp. Mol. Cell. Biol., New Ser., v. 82, pp. 313-326 (1988)) as applied to claims 27, 28, 30, 31, 34-36, 39-41, and 48-50 above, and further in view of Akli et al. (1993) Nat. Genet. **3**: 224-228.

Neither McClelland et al. nor Mullenbach et al. teach that the DNA of interest could be operably linked to the RSV-LTR promoter or that glial cells could be infected.

However, Akli et al. taught that replication-deficient, recombinant adenovirus can infect glial cells (astrocytes) and that RSV-LTR promoter could be used to direct transcription of DNA of interest in transfected cells.

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have substituted the promoter for the DNA encoding the glutathione peroxidase with the RSV-LTR promoter of Akli et al. in the invention of McClelland et al. and Mullenbach et al. with reasonable expectation of success and because the promoters had been used in the prior art to express DNA in the appropriate host cells, and the RSV-LTR promoter had been used for that purpose in replication-deficient, recombinant adenovirus, and to transfect glial cells, because of the express teaching in Akli et al. that replication-deficient, recombinant adenovirus can infect glial cells.

Certain papers related to this application may be submitted to Art Unit 1819 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993)

and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, Ph.D., can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SDP

Scott D. Priebe, Ph.D.
Examiner

January 8, 1998

Jasemine C. Chambers

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